IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application No. 09/693,121

Applicant: Jeffrey Schlom

Filed: October 20, 2000

TC/AU: 1643

Examiner: Christopher H. Yaen

Docket No.: 701319 (Client Reference No. E-200-1990/4-US-06)

Customer No.: 45733

Title: GENERATION OF IMMUNE RESPONSE TO PROSTATE-SPECIFIC ANTIGEN (PSA)

DECLARATION UNDER 37 C.F.R. § 1.131

We, Jeffrey Schlom and Dennis Panicali, hereby declare the following:

1. We are co-inventors in the above-captioned patent application.

2. Prior to August 11, 1993, we had conceived of a method for generating a cytotoxic T-cell eliciting immune response to prostate specific antigen (PSA) in a human host, by first administering a pox virus vector containing an insertion site for DNA encoding PSA or a cytotoxic T-cell eliciting epitope thereof and then administering an additional PSA or T-cell eliciting epitope thereof.

3. Exhibit A is a Material Transfer Agreement (MTA). While the date of the MTA has been redacted, we executed the MTA prior to August 11, 1993. The MTA demonstrates that we intended to use recombinant vaccinia and fowlpox vectors with a human tumor-associated antigen gene inserted therein to produce clinical grade vaccine.

4. Exhibit B is another Material Transfer Agreement (MTA). Again, while the date of the MTA has been redacted, we executed the MTA prior to August 11, 1993. The MTA demonstrates that we intended to use a prostate specific antigen (PSA) clone in the production of clinical grade vaccine.

5. Exhibit C constitutes relevant portions of an Agenda for a site visit at the Laboratory of Tumor Immunology and Biology. While the date recited in this document has been redacted, the site visit was scheduled prior to August 11, 1993. Studies involving the use of rV-PSA in nonhuman primates are detailed on page 40 of this document. These studies include implementation of a "prime and boost" strategy. As stated in the document, "We will prime mice who have a palpable tumor with rV-PSA and then boost with varying concentrations of either bV-PSA or immunogenic PSA peptides emulsified with DETOX or liposomes." We planned on studying the growth of the tumor and the effect on cell mediated responses such as PSA specific lymphoproliferative responses and cytotoxic T cell responses. Exhibit C further sets forth our plan to utilize recombinant avipox-PSA and recombinant PSA protein to induce the generation of $CD4^+$ and/or $CD8^+$ T cells.

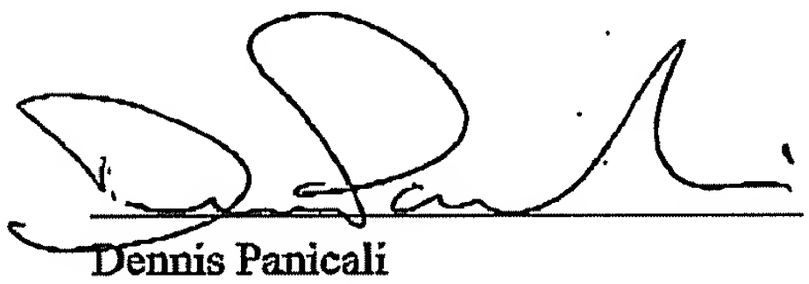
In re Appln. of Schlom et al.
Application No. 09/693,121

6. We hereby declare that all statements made herein of our own knowledge are true, that all statements made on information and belief are believed to be true, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____

_____
Jeffrey Schlom

Date: OCT. 5, 2007



Dennis Panicali

EXHIBIT A

National Institutes of Health
Alcohol, Drug Abuse and Mental Health Administration

Material Transfer Agreement

This Material Transfer Agreement ("MTA") has been adopted for use by the National Institutes of Health ("NIH") and the Alcohol, Drug Abuse and Mental Health Administration ("ADAMHA") in all transfers of research material ("Research Material") whether NIH or ADAMHA is identified below as its Provider or Recipient.

1.) Provider agrees to transfer to Recipient's investigator named below the following Research Material:

a) Vaccinia recombination vector pABT 4587 b) fowlpox recombination vector pABT 2330

2.) This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

A human tumor associated antigen gene will be inserted into the vector, characterized and returned for clinical grade vaccine production.

3.) **THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS.** This Research Material will only be used for research purposes by Recipient's investigator in his/her laboratory under suitable containment conditions. This Research Material will not be used for commercial purposes such as screening, production or sale, for which a commercialization license may be required. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material. Unvaccinated individuals who are pregnant, suffer from eczema or other chronic skin disorders or have altered (deficient) immune status should not be exposed to vaccinia. Vaccinia can cause grave health problems in such individuals.

4.) In all oral presentations or written publications concerning the Research Project, Recipient will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat in confidence, for a period of three (3) years from the date of its disclosure, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL," except for information that was previously known to Recipient or that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given CONFIDENTIAL information to Recipient such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure, except when a shortened time period under court order or the Freedom of Information Act pertains.

5.) This Research Material represents a significant investment on the part of Provider, and is considered proprietary to Provider. Recipient's investigator therefore agrees to retain control over this Research Material, and further agrees not to transfer the Research Material to other people not under her or his direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and use it for its own purposes. When the Research Project is completed, or three (3) years have elapsed, whichever occurs first, the Research Material will be destroyed by Recipient or otherwise disposed of as mutually agreed by Provider and Recipient.

6.) This Research Material is provided as a service to the research community. **IT IS BEING SUPPLIED TO RECIPIENT WITH NO WARRANTIES, EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY OR MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE.** Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

7.) When Provider is the NIH/ADAMHA: Recipient shall retain title to any patent or other intellectual property rights in inventions made solely by its employees in the course of the Research Project. Recipient agrees not to claim, infer, or imply Governmental endorsement of the Research Project, the institution or personnel conducting the Research Project or any resulting commercial products(s). Recipient agrees to hold the United States Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material. Recipient shall have joint title with Provider to any patent or other intellectual property right in inventions invented jointly by its employees and provider employees as determined in accordance with applicable U.S. Patent law.

8.) When Recipient is the NIH/ADAMHA: The NIH/ADAMHA shall retain title to any patent or other intellectual property rights in inventions made solely by its employees in the course of the Research Project. The NIH/ADAMHA are not authorized to promise rights in advance for inventions developed through this Research Project, except under a Cooperative Research and Development Agreement ("CRADA") pursuant to the Federal Technology Transfer Act of 1986. Except as may be accorded through Paragraph 9, below, Provider acquires no intellectual property rights under this MTA, but may apply for license rights to any patentable invention that might result from this Research Project. It is the intention of NIH/ADAMHA that Provider not be liable to NIH/ADAMHA for any claims or damages arising from NIH/ADAMHA's use of the Research Material, however, no indemnification is provided or intended. Recipient shall have joint title with Provider to any patent or other intellectual property right in inventions invented jointly by its employees and provider employees as determined in accordance with applicable U.S. Patent law.

9.) Pursuant to their "Policy Statement on Cooperative Research and Development Agreements and Intellectual Property Licensing, "NIH and ADAMHA may permit their investigators to enter into CRADAs (and thereby promise an option to acquire intellectual property rights) in exchange for the contribution of "essential research materials...not otherwise reasonably available." If the Research Material transferred by this MTA is so certified below, Provider and the NIH/ADAMHA (when Recipient) investigator should submit a formal CRADA for NIH/ADAMHA approval. For nongovernmental entities that regularly provide research materials to NIH or ADAMHA, it is suggested that a master CRADA be negotiated under which a certification below will suffice to invoke the provisions of the CRADA. If Provider and Recipient otherwise decide to engage in a cooperative research or development project using the Research Material, a formal CRADA must also be negotiated. For general inquiries regarding CRADAs or NIH/ADAMHA technology transfer policies, contact the Office of Invention Development at (301) 496-0750.

For receipt of Research Material under this Paragraph, when a master CRADA governing material transfers is in effect between NIH or ADAMHA and Provider, the NIH/ADAMHA investigator must identify the CRADA by NIH/ADAMHA reference number:_____, and provide a more detailed description than in Paragraph 2, above, of the specific extent of activities within the overall Research Project to which the provisions of the CRADA will pertain (use an attachment page if necessary). Signature by the investigator and authorized official below constitutes certification that the Research Material transferred by this MTA is essential and not otherwise reasonably available for the following activities:

_____

_____

10.) This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11.) Any additional terms: The undersigned expressly certifies or affirms that the contents of any statements made or reflected in this document are truthful and accurate. This material is for research purposes only. It is not to be used for any clinical or diagnostic purposes or to be given to any third parties.

Date:

Dr. Jeffrey Schlom, Chief, LTIB
authorized signature for Provider and Title

Recipient's mailing address:

National Institutes of Health
National Cancer Institute
Laboratory of Tumor Immunology & Biology
Bldg. 10, Room 8B07
9000 Rockville Pike
Bethesda, MD 20892

Date.

Dennis Panicali, President
Provider's Investigator and Title

Date:

authorized signature for Provider and Title

Provider's mailing address:

Therion Biologics Corporation

76 Rogers Street

Cambridge, MA 02142

Tel: (617) 876-7779

EXHIBIT B

tional Institutes of Health
Alcohol, Drug Abuse and Mental Health Administrat...

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1.) Provider agrees to transfer to Recipient's investigator named below the following Research Material:

a) ras (gly → CYS) clone b) PSA clone

2.) This Research Material will be used by Recipient's investigator solely in connection with the following research project ("Research Project") described with specificity as follows (use an attachment page if necessary):

Reagents will be used in the production of clinical grade vaccine only per the terms of the NCI contracts (Task A).

3.) THIS RESEARCH MATERIAL MAY NOT BE USED IN HUMAN SUBJECTS. This Research Material will only be used for research purposes by Recipient's investigator in his/her laboratory under suitable containment conditions. This Research Material will not be used for commercial purposes such as screening, production or sale, for which a commercialization license may be required. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

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8.) When Recipient is the NIH/ADAMHA: The NIH/ADAMHA shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. The NIH/ADAMHA are not authorized to promise rights in advance for inventions developed through this Research Project, except under a Cooperative Research and Development Agreement ("CRADA") pursuant to the Federal Technology Transfer Act of 1986. Except as may be accorded through Paragraph 9, below, Provider acquires no intellectual property rights under this MTA, but may apply for license rights to any patentable invention that might result from this Research Project. It is the intention of NIH/ADAMHA that Provider not be liable to NIH/ADAMHA for any claims or damages arising from NIH/ADAMHA's use of the Research Material, however, no indemnification is provided or intended.

9.) Pursuant to their "Policy Statement on Cooperative Research and Development Agreements and Intellectual Property Licensing, "NIH and ADAMHA may permit their investigators to enter into CRADAs (and thereby promise an option to acquire intellectual property rights) in exchange for the contribution of "essential research materials...not otherwise reasonably available." If the Research Material transferred by this MTA is so certified below, Provider and the NIH/ADAMHA (when Recipient) investigator should submit a formal CRADA for NIH/ADAMHA approval. For nongovernmental entities that regularly provide research materials to NIH or ADAMHA, it is suggested that a master CRADA be negotiated under which a certification below will suffice to invoke the provisions of the CRADA. If Provider

and Recipient otherwise decide to engage in a cooperative research or development project using the Research Material, a formal CRADA must also be negotiated. For general inquiries regarding CRADAs or NIH/ADAMHA technology transfer policies, contact the Office of Invention Development at (301) 496-0750.

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10.) This MTA shall be construed in accordance with Federal law as applied by the Federal courts in the District of Columbia.

11.) Any additional terms: The undersigned expressly certifies or affirms that the contents of any statements made or reflected in this document are truthful and accurate. This material is for research purposes only. It is not to be used for any clinical or diagnostic purposes or to be given to any third parties.

Date: _____

Dennis Panicali, Ph.D, President
Recipient's Investigator and Title

Date:

authorized signature for Recipient and Title

Recipient's mailing address:

Therion Biologics Corp.
76 Rogers Street
Cambridge, MA 02142

Date:

Jeffrey Schlom, Ph.D., Chief, Laboratory of Tumor Immunology and Biology
Provider's Investigator and Title

Date:

Dr. Jeffrey Schlom, Chief, LTIB
authorized signature for Provider and Title

Provider's mailing address:

National Institutes of Health
National Cancer Institute
Laboratory of Tumor Immunology & Biology
Bldg. 10, Room 8B07
9000 Rockville Pike
Bethesda, MD 20892

EXHIBIT C

BOARD OF SCIENTIFIC COUNSELORS
DIVISION CANCER BIOLOGY, DIAGNOSIS, AND CENTERS
NATIONAL CANCER INSTITUTE

SITE VISIT AGENDA

Laboratory of Tumor Immunology and Biology

IRRELEVANT MATERIAL REDACTED

IRRELEVANT MATERIAL REDACTED

III. ACTIVE SPECIFIC IMMUNOTHERAPY USING PROSTATE SPECIFIC ANTIGEN (PSA) AS A TARGET.

ESTABLISHMENT OF AN ANIMAL TUMOR MODEL EXPRESSING PSA. We plan to first introduce the PSA gene into MC-38 murine colon adenocarcinoma cells (86). As described above, no rodent prostate carcinoma cell line expressing PSA has been established. The MC-38 cell line potentially represents an excellent recipient of the PSA gene. Our previous studies with this cell line demonstrated transduction with a retroviral construct containing cDNA encoding the human CEA gene (86)

If the tumor model can be established and characterized we will begin a series of animal studies that will address the issue of whether PSA is a potential target for ASI. Even though PSA does not appear on the surface of the cell it still may be a good target for ASI. One must also consider that cytoplasmic and nuclear proteins are processed by the cell and are represented on the surface as peptides, usually in the context of the MHC molecules (118). Doses and routes of injection for maximum biological effect of rV-PSA and bV-PSA will be determined. Prevention studies will be performed where animals will be immunized 1, 2, 3, or 4 times with either the recombinant vaccinia PSA or with recombinant PSA emulsified in DETOX or with both immunogens in a prime and boost sequence. The effect on the growth of transplanted PSA(+) and PSA(-) tumor cells will be evaluated. Therapy studies using established tumors will also be performed. PSA (+) and (-) tumor cells will be subcutaneously transplanted and established tumors will be treated by either immunizing the animal with the PSA recombinant vaccine or with recombinant PSA protein. We will also analyze specific immune responses that may be elicited by these immunogens. If no tumor model can be established, humoral and cell mediated responses such as DTH, PSA specific lymphoproliferative responses and CTL responses will be defined in immunized animals.

Immunogenicity and safety of the rV-PSA will be performed in non human primates as detailed in our studies with recombinant CEA vaccines. As we have described above for our studies with recombinant CEA vaccines, we will also carry out studies on the use of cytokines to enhance specific anti-PSA T cell responses. In the event that the rV-PSA alone does not inhibit tumor growth we

will try other immunization approaches to enhance the immune response. These include "prime and boost". We will prime mice who have a palpable tumor with rV-PSA and then boost with varying concentrations of either bV-PSA or immunogenic PSA peptides emulsified with DETOX or liposomes. Our long range plans will in part be dictated by our results with various vectors and peptide structures using recombinant CEA and point mutated ras vaccines. The principles learned will be translated to the PSA studies as well as studies using recombinant vaccines containing other tumor associated antigens.

IRRELEVANT MATERIAL REDACTED

IRRELEVANT MATERIAL REDACTED

B. **Human**

Clinical Trials

If preclinical studies are promising, then clinical trials with rV-PSA and the recombinant PSA protein will be considered. In collaborative phase I trials, in patients that had undergone a prostatectomy and have metastatic prostate cancer, we will attempt to characterize their immune responses before, during and after ASI with rV-PSA, alone or in combination with PSA protein/peptide boosting, and correlate functional responses in vitro with potential changes in the clinical course of disease. The details of these studies will be as described above for the clinical trials with the CEA vaccines.

Generation of CEA-Specific $CD4^+$ and/or $CD8^+$ T Cells

Since PSA is a tumor-associated Ag and immunogenic epitopes are unknown, we propose to adopt a similar strategy to that of CEA for in vitro restimulation of in vivo-primed T lymphocytes for the potential propagation of $CD4^+$ and/or $CD8^+$ cells. Therefore, for $CD8^+$ cells, we will exploit a recombinant avipox-PSA construct, whereas for $CD4^+$ cells, we will utilize recombinant PSA protein. $CD4^+$ and/or $CD8^+$ T cell lines and clones established in culture will be evaluated for functional activity (i.e., proliferation, cytokine production or cytotoxicity) following stimulation with synthetic peptides for the identification of putative immunodominant epitopes. In the interest of brevity, the detailed analysis of the immune response mechanism will be conducted as described for the rV-CEA studies.

IRRELEVANT MATERIAL REDACTED